Assessment and management of childhood skeletal malignancies

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Abstract

Primary bone cancers are a rare but life changing diagnosis. Early diagnosis and onward referral to a multidisciplinary team within a dedicated sarcoma centre is associated with the best outcomes. The most common lesions, osteosarcoma and Ewing's sarcoma, are aggressive tumours with a tendency to metastasize to the lungs. Treatment for localized and some metastatic cases generally consists of multiagent neoadjuvant chemotherapy followed by surgical resection and reconstruction prior to further chemotherapy. In spite of advances in surgical technique and chemotherapy regimes, overall five-year survival remains approximately 50–60%.

Keywords child; Ewing's sarcoma; osteosarcoma

Introduction

In 2013, there were only 582 newly diagnosed sarcomas of bone in the UK[1] and, as such, primary bone malignancies are a rare entity. Primary bone cancers account for less than 1% of all malignancies, however in children this figure is higher (~5% of all malignancies).[1,2] This makes them unfamiliar to most clinicians, including many experienced Orthopaedic surgeons. It is, therefore, helpful to have a robust system to avoid missing or mistreating malignant lesions of bone, to avoid a negative impact on long-term survival and function. Accurate initial diagnosis is vital to allow definitive treatment to take place at one of a small number of tertiary centres where clinicians can offer more standardized care and clear guidance should be in place to access their regional referral pathways.

The name "Sarcoma" derives from the Greek, *sarx* meaning flesh and *oma* meaning swelling, and refers to a malignant tumour of the musculoskeletal (mesenchymal) tissues, as opposed to the common solid organ carcinomas derived from ectodermal tissues with common sites including breast, prostate, lung and bowel. Osteosarcoma and Ewing's sarcoma are by far the most common primary bone cancers in children and are the focus of this review. The principles of assessment and treatment are largely applicable to the other rarer tumours.

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Demographics

Unlike soft-tissue sarcomas, the incidence of bone sarcomas follows a bimodal distribution, with a significant peak close to the timing of the adolescent growth spurt. There is a slight male preponderance (1.7: 1).[3] Over half of childhood primary bone cancers are osteosarcomas and at least a third are Ewing's sarcomas. The remainder of cases is a mixture of rarer subtypes such as adamantinoma. Unlike in adults, chondrosarcoma is rarely seen in childhood. Under the age of five years, primary bone cancers are rarely seen, and metastatic neuroblastoma, leukaemia or eosinophilic granuloma are more likely causes of a painful destructive lesion of bone.[4]

Giant Cell Tumours (GCTs) warrant special mention as they fall within the category of benign tumours which have the potential for rare metastatic spread to the lungs (2%) and occasional malignant transformation.

Biology and genetics

Skeletal tumours are classified by the WHO according to their tissue of origin and matrix production as Chondrogenic (cartilage forming), Osteogenic (bone forming), Osteoclastic, Giant Cell Rich, Vascular, Fibrohistiocytic, Notochordal and Uncertain Differentiation.[5] The greatest number is derived from abnormal cells within the mesenchymal stem cell line. Ewing's sarcoma is unusual in that it seems most closely related to the primitive neuroectodermal tissue and has the same genetic changes as Primitive Neuroectodermal Tumours (PNETs). The sequence of tumour genesis to form Ewing's tumours in bony locations is currently poorly defined.

Modern genome analysis techniques have vastly expanded our knowledge of sarcoma cell lines and translocations. Eighty-five percent of Ewing tumour cases express the EWS-FLi1 fusion protein formed by a translocation of chromosome 11 and chromosome 22 (t11;22).[6] In the future, targeting of specific cell may lead to novel therapies and modified treatment algorithms. Osteosarcoma has been extensively studied and found to have a fundamentally more complex and heterogeneous genotype.[7] A number of the soft tissue sarcomas have clearly defined translocations but this is beyond the scope of this review.

Whilst the genetic changes are similar in many tumour types, they are mostly not inherited conditions; the genetic mutations typically occur *de novo*. A small number of patients may be more at risk due to a heritable cancer syndrome. For example, Li Fraumeni families have a mutation of the tumour suppressor p53 rendering them at risk of breast malignancies, osteosarcomas, soft tissue sarcomas and leukaemia.[8] Carriers of an abnormal retinoblastoma gene are also at risk of osteosarcoma (RB1).[9] There are some conditions, such as multiple enchondromatoses (Ollier's/Mafucci syndromes) and Hereditary Multiple Exostoses (HMEs), which have an increased risk of the transformation of a benign chondroid lesion into a chondrosarcoma. Interestingly, Ollier's and Mafucci syndromes are not inherited conditions and in all cases have non-germline mutations with a tendency to show genetic mosaicism. Lifetime risk of malignant transformation is very variable in the literature, however a recent international retrospective review through the European Musculoskeletal Society found an incidence of chondrosarcoma of 40% in 144 Ollier and 17 Mafucci patients. Families with Hereditary Multiple Exostoses pass on the EXT1, EXT2 or EXT3

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genes in an autosomal dominant manner. Current practice favours annual clinical assessment and re-imaging of painful or growing lesions. A cartilage cap thickness of 2 cm is strongly predictive of secondary chondrosarcoma.[10]

There are few proven predisposing environmental factors for childhood bone sarcoma, however radiotherapy induced sarcoma is a well-described, if rare, complication of treatment of other neoplasms.

Making a diagnosis

Primary bone tumours are easily missed! The most important tool to avoid a serious delay in diagnosis is to have a high index of suspicion. Data from the Royal Orthopaedic Hospital in Birmingham show that the average size of bone sarcomas at diagnosis 11.3 cm.[11] This correlates with a lower chance of survival, and on this measure the UK performs poorly. The mean tumour size in children is very similar to adults for bone sarcomas. Average time to diagnosis from onset of first symptoms is 16 weeks[11] and this has not improved significantly from the National Cancer Intelligence Network data.

Take a detailed history

The classic symptoms of bone tumours are a constant pain, disturbing sleep at night and restricting activity. Whilst non-specific, these features should prompt more detailed enquiry, particularly if they last for more than a few weeks. Duration, character, precipitants and night pain should be recorded. Systemic features including fever and weight loss may be a feature. If symptoms have been present for some time prior to presentation, a number of treatments may have been tried. There may be a history of recent injury but this should be assessed with caution, as children and their families will frequently try to attribute symptoms to an event which may not be causally linked. In addition, be wary of a history of chronic or non-resolving haematoma, which may be more that it seems on face-value.

Regardless of the age of a child, a complete history should begin at birth and include previous medical and surgical treatments, family traits and developmental progress. A background social history may help to identify requirements for extra services and support should a sinister diagnosis be revealed.

Focused examination

Expose the limb or body part adequately to ensure that the full extent of any swelling is seen and compared to the other side. As with any lump, pay attention to the size, texture, mobility and fixity to adjacent structures. Observe for deformity and leg length discrepancy, and for presence of kyphoscoliosis in the presence of spinal lesions. Local, regional and distant lymph nodes should be examined, together with the liver and spleen, particularly to gather information on alternative differential diagnoses such as lymphoma. Crucial information regarding possible involvement or pressure on crucial structures may be obtained by a careful neurovascular examination, including Tinel's tapping test over the lesion and nearby nerves (Box 1).

Imaging

All patients with unexplained pain or a mass should have plain radiographs taken of the whole bone including orthogonal views up to the joint above and below the area of interest (Box 2).

Clinical features of concern for sarcoma

- Unexplained pain
- Night or mechanical pain
- New lump >5 cm or growing lump of any size
- Rapid increase in size
- Lump felt deep to fascia

Box 1

Plain radiographic features of sarcoma

- Bone destruction
- New bone formation
- Periosteal reaction
- Soft tissue swelling

Box 2

Some typical radiographic appearances or Osteosarcoma and Ewing's sarcoma are shown in Figures 1 and 2. The absence of radiographic abnormality does not exclude a diagnosis of sarcoma and in the presence of concerning symptoms, further imaging is required, usually a Magnetic Resonance (MRI) scan.

The site may give a clue to tumour type. Osteosarcoma classically affects the metaphysis of long bones, particularly the distal femur and proximal humerus. Ewing's sarcoma has a predilection for the diaphysis. Tumours which remain adequately differentiated tend to lay down identifiable matrix with the appearances of their tissue of origin and the typical patterns of osteoid or chondroid mineralization can be helpful to identify the tumour on plain films. Bone lesions should be reviewed by an experienced musculoskeletal radiologist and

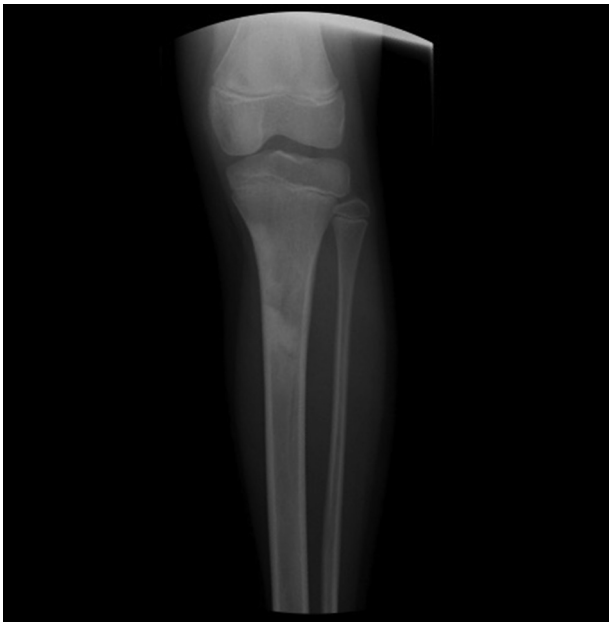

Figure 1 Plain AP radiograph of 9-year-old child with osteosarcoma. Note the bone forming lesion with patchy lysis and permeative margins.

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